ICH STEERING COMMITTEE
May 5-10, 2007, Brussels, Belgium
SUMMARY

1. Opening Discussions
The ICH Steering Committee (SC) meeting was chaired by EU. The meeting commenced with the provision of updates on the work of the ICH Secretariat, MedDRA and the Global Cooperation Group (GCG).

ICH Secretariat: The ICH Secretariat reported on work undertaken to improve communications with ICH stakeholders. As of March 6, 2007, the ICH Secretariat posted new web pages for the ICH Concept Papers and Business Plans. The web pages were reorganized and redesigned to accommodate the addition of a “new batch” of older Concept Papers and Business Plans to the ICH website. The ICH Secretariat will gradually continue to add all Final Concept Papers and Business Plans. The summarized ICH SC Report for Chicago 2006 was also published on the ICH public website.

MedDRA: The Chair of the MedDRA Management Board reported on the decisions taken by the Board on behalf of the ICH SC. To underpin the role of MedDRA in public health, the Board confirmed its long-term commitment to provide MedDRA free to direct patient care providers such as hospitals and individual health care providers involved in non-commercial activities, for the purpose of adverse event reporting.

The SC noted that there had been a major reduction in the 2006 and 2007 subscription fees, with a greater reduction for the low revenue subscribers, especially Core 0, Core 1 and Core 2 levels that correspond to small and medium-sized enterprises. This reduction was seen as being the likely reason for the large increase in the number of low revenue subscribers at the Basic, Core 0, Core 1 and Core 2 levels. For the last 12 months, new subscribers represented 28% of total MSSO subscribers, and as of March 2007, 10% of all MSSO subscribers.

The Chair informed the SC that the 2008 subscriber fee structure would be decided upon by mid-2007, however no increase in fees was expected across all core levels and it was hoped that it might be possible to further decrease the fee structure for the low-end revenue subscribers.

The Chair also reported that the Board had agreed to provide support to accelerate the integration of MedDRA into the WHO Global Database (Vigibase). The integration will allow MedDRA coded data to be entered and retrieved in their original format. The project with the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, Sweden), which was initiated in February 2007 is due for completion in March 2008.
At the Brussels meeting, the Board endorsed the renewal of the Memorandum of Understanding between ICH (IFPMA) and CIOMS (Council for International Organizations of Medical Sciences) for the development by the CIOMS Working Group of Standardised MedDRA Queries (SMQs). SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The Chair informed the SC that as of May 2007, 53 SMQs had been finalized by the CIOMS WG, 43 of which were already available to subscribers. The SC noted that the 60 most common SMQs will have been developed by May 2008.

The SC noted that the Czech translation of MedDRA would be available with the release of MedDRA 10.1 in September 2007, and that it was expected that Hungarian and Lithuanian translations of MedDRA would be made available in 2008. This would add to the French, German, Portuguese, Spanish, Dutch and Italian already available, in addition to the English and Japanese translations. In addition, recognizing the importance of engaging with non-ICH countries that are becoming increasingly involved in clinical trials and production of pharmaceutical products, the Board gave their approval for a Mandarin Chinese translation of MedDRA.

Global Cooperation Group: The GCG Co-Chairs reported to the SC on the activities of the GCG meeting. Participants in attendance from the regional harmonisation initiatives (RHIs) included representatives from APEC, ASEAN, GCC, PANDRH and SADC.

The report included feedback from a Brainstorming Session that was held with the GCG and RHIs to understand the views of RHIs on the value of attending the GCG and ICH Expert Working Groups (EWGs). The session highlighted many useful points, and was found to be very beneficial to all participants.

The SC noted that the GCG was in the process of coordinating two requests for training from APEC. One was a request for a Q8, Q9 and possibly Q10 workshop, to be held in Seoul, Korea, in September 2007, and the other was a request for workshops on Clinical Trial assessment and GCP inspection to be held in Thailand in 2007 and 2008. Each of the ICH Parties were requested to confirm their interest to provide speakers.

2. Proposals for New Topics and Revisions/Maintenance of Guidelines

Maintenance of ICH Controlled Terminology Lists:

The Rapporteur presented an update to the SC on the maintenance process for ICH terminology lists. The SC noted that several lists (Tables of thresholds for Q3A(R2) and Q3B(R2), List of solvents and PDE for Q3C(R3), virus detected in antibody tests for Q5A(R1), listing of base set for S2A, data elements in clinical study reports for E3, list of essential documents for E6(R1), and list of key elements for inclusion in expedited reports for E2A) were proposed to be maintained through the previously developed Change Control Process with the involvement of Rapporteurs and the ICH Secretariat. It was noted that no list had yet gone through this maintenance process and there was some discussion about the practicalities of the process. The SC
requested that the Rapporteur review the process and consider whether it can be streamlined.

In Chicago, in October 2006, the SC approved that E2B(R) and M5 messages enter the SDO (Standards Development Organisation) process for development by a Consortium that would be composed of ICH, the International Organisation for Standardisation (ISO), Health Level 7 (HL7) and the European Committee for Standardisation (CEN). The New Work Item Proposals for the E2B(R) and M5 messages were sent to ISO in February 2007 (see below for discussion for M2).

Recommendations concerning the method(s) and organization(s) that will be responsible for ongoing maintenance of the M5 Controlled Vocabularies will be included in the work plan of the ISO Task Force (see below for discussion for M5). It was noted that a decision about the maintenance organization would need to be made prior to publication of the ISO standard. Maintenance factors will be specific to each standard such as scope, complexity and frequency of update.

**Quality Strategy Discussion:** Further to the first strategy discussion that was held in Chicago, in October 2006, the SC received a report on the outcome of the Quality Strategy Discussion that was held in Brussels in order to work out a harmonized quality strategy and a work plan.

The SC supported the group’s recommendation to establish an informal Implementation Working Group (IWG) to evaluate the need for a formal IWG that would be tasked with assuring globally consistent implementation and sharing of best practices. The informal IWG will be tasked with identifying regional issues, potential implementation topics and preparing the agenda for Yokohama.

The SC also endorsed FDA/PhRMA to organize an ICH meeting in Washington D.C. of Chemical and Biotech experts to take place prior to the October 2007 Yokohama meeting. The aim of the meeting will be to discuss similarities and differences between chemical and biotech drug substances, and to assess key elements of Q8, Q9, Q10 and their applicability to drug substance development. The results of the technical assessment will be reported to the SC in Yokohama in October 2007.

**Interface with VAM Groups:**

The SC received a report on the outcome of a meeting held in Brussels between ICH non-clinical safety experts and representatives from the CVAMs (Centers for the Validation of Alternative Methods) of the three ICH regions. The objective of the meeting was for the ICH experts to be updated on ongoing activities regarding alternative methods to animal testing and to increase mutual understanding and collaboration.

The meeting was in line with ICH’s commitment to the "three Rs" agenda, with a view to Reduce/Refine/Replace animal testing when drafting new or revising existing guidelines.

**Oncology Therapeutics:**
The Oncology Therapeutics Informal Working Group did not meet in Brussels, but provided the Oncology Therapeutics Concept Paper and Business Plan for SC consideration. The SC approved the Concept Paper and Business Plan, and endorsed the establishment of a formal EWG. The topic code for this new ICH guideline was confirmed to be S9. It was agreed that the first meeting of the S9 EWG would take place in Yokohama in October 2007.

3. Reports on Current Topics

Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD (Topic M2 / eCTD): In Chicago, in October 2006, the SC agreed that the E2B(R) and M5 messages enter the SDO process for development by a Consortium that would be composed of ICH, the International Organisation for Standardisation (ISO), Health Level 7 (HL7) and the European Committee for Standardisation (CEN). At the Brussels meeting, the SC was updated by the Rapporteur on the SDO process to date.

In February 2007, the E2B(R) and M5 messages were submitted to ISO in the form of seven New Work Item Proposals (NWIPs), which were subsequently accepted for ballot by ISO TC 215 (ISO’s Technical Committee on Health Informatics). At the ISO meeting held in Montreal, in March 2007, it was agreed that the seven NWIPs would be taken up as two main areas of work, with the creation of a Pharmacovigilance ISO Task Force and an Identification of Medicinal Products ISO Task Force. Both Task Forces would be led by ICH experts.

In addition, ICH was granted category D liaison status within ISO, which allows ICH to submit work items and participate actively in Working Groups.

The Rapporteur informed the SC of the continued development of the relationship between ISO, CEN, and HL7, for which a charter had been developed to put into place high-level processes and governance structures. With the establishment of this “Joint Initiative”, it was noted that a formal relationship (e.g. establishment of a Memorandum of Understanding) with HL7 or CEN would not be necessary, as the formal relationship of ICH with the SDOs would be through the liaison with ISO.

In order to evaluate the SDO process, the SC tasked the M2 EWG to with the development of a paper on success criteria, for consideration by the SC. It was agreed that the M2 SDO sub-group should closely monitor the pilot project and that the M2 Rapporteur should report regularly to the SC.

The Rapporteur also reported to the SC on the work of the M2 eCTD sub-group. The SC endorsed the e-CTD Specification version 3.3.3 Step 2 for Testing Release Package. The package would be made available on the ESTRI website (on the ICH website), and regional testing would be conducted with a deadline for comments by 28 September 2007. A new version of the Change Request/Q&A document was also endorsed by the SC.

M5: Data Elements and Standards for Drug Dictionaries: The Rapporteur updated the SC on the activities of the M5 EWG. Since the Chicago meeting, in October 2006, the M5 EWG finalized the ICH M5 business requirements for five New Work Item
Proposals (NWIPs) that were submitted to ISO in February 2007 (see also above discussion for M2). In addition, the EWG prepared the draft M5 Step 4 Guideline as a supporting document for the five NWIPs.

The Rapporteur sought SC guidance on the rules of engagement related to the drafting of ICH requirements in the SDO process for the controlled vocabularies for the remaining drug substance classes and for terminology maintenance. The SC agreed that the scope of the remaining drug substance classes to be advanced to the ISO process include hormones, enzymes, recombinant coagulation factors, albumins, recombinant allergens, toxins, human interferons and gene therapy. The SC also agreed that the consensus building process regarding the development of key requirements for terminology maintenance take place within the SDO process.

The SC supported the M5 EWG’s proposal to organise monthly teleconferences of M5 with the ISO Task Force leader on the Identification of Medicinal Products Topic, the M2 Rapporteur and the M2 Task Force Members to consult on the outcome of Task Force meetings, to review ICH input in project definition and plan, and to define ICH input in the next steps of the project. This would ensure the continuous flow of information, and coordination of ICH input.

**E2B(R3): Revision of the Electronic Submission in Individual Case Safety Reports:** The Rapporteur updated the SC on the activities of the E2B(R3) EWG. Since the Chicago meeting, in October 2006, the E2B(R3) EWG finalized the ICH E2B(R) business requirements for two New Work Item Proposals (NWIPs) that were submitted to ISO in February 2007 (see also above discussion for M2). In addition, the EWG updated the draft E2B(R3) Step 4 guideline as a supporting document for the two NWIPs. The SC agreed that the document would not reach Step 4 until the outcome of the SDO process.

It was noted that although the requirements for the maintenance of M5 controlled vocabularies would undergo a consensus-building process within ISO (see above discussion for M5), the M2 EWG would work with both the M5 and E2B(R3) EWGs in the development of their respective implementation guides, which would be customized to ICH needs.

The SC supported the E2B(R3) EWG’s proposal to organise monthly teleconferences of E2B(R3) to ensure the continuous flow of information, and to facilitate consultation of the Task Force outcome.

**Pharmacopoeial Discussion Group:** On behalf of the Pharmacopoeial Discussion Group (PDG), the European Pharmacopoeia (EP) reported on the current status of PDG harmonisation efforts.

Harmonisation has been achieved on ten of the eleven General Chapters related to the ICH Q6A Guideline. The Stage 4 draft of the General Chapter on Color (Instrumental Measurement) is currently in preparation, while the Stage 4 draft of the harmonised Bacterial Endotoxins Chapter (revision) is currently out for comments in the three regions.
The SC was also provided an update on the status of submitted packages. The Q4B EWG considered interchangeable the Residue on Ignition/Sulphated ash. The PDG eliminated all residual differences on Sterility test, identified by the Q4B EWG. The sign-off of the revised text is expected at the next meeting.

The PDG submitted to the Q4B EWG the harmonized texts on Particulate Matter in Injectables and on Dissolution. The PDG would send a formal reply to comments received from the Q4B EWG on both texts by July 2007. The PDG was awaiting the Q4B EWG evaluation of the harmonized text on Extractable Volumes of Parenterals, Disintegration Test and Uniformity of Dosage Units. The PDG will submit three Chapters on Microbiological Quality to the Q4B before the end of May 2007.

The SC was also informed that PDG members and the WHO had agreed to collaborate in the establishment of the next batch of Bacterial Endotoxin Reference Standard. The batch will serve as a future common batch for an International Standard, a USP standard and an EP standard.

**S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use:** In Chicago, in October 2006, the SC supported the proposal of the S2(R1) EWG to merge the S2A and S2B guidelines during the revision of these guidelines. Following the meeting the new title of the guideline was confirmed as S2(R1), Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use.

The Rapporteur reported to the SC on the progress of the S2(R1) EWG in Brussels. The EWG took into consideration the 3Rs (Reduce/Refine/Replace) principle for genotoxicity studies. The numbers of animals used in in vivo genotoxicity studies would be reduced whenever possible without impacting on the scientific value of the tests and the evaluation of human risk.

The Rapporteur presented two options for the new standard battery that seemed according to the experts equally acceptable to detect relevant genotoxicity. The new requirements will reduce the number of in vivo (stand alone and follow up) genotoxicity studies, and therefore the number of animals.

The SC noted that S2(R1) Step 2 was expected to be reached at the next meeting in Yokohama in October 2007.

**M3(R2): Revision of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals:** The Rapporteur updated the SC on the work of the M3(R2) EWG. The group reached consensus on exploratory FIM (first-in-man) nonclinical toxicology packages, and all of the approaches will have a positive impact on the 3Rs (Reduce/Refine/Replace) principle. Consensus was also reached on the maximum duration of chronic testing in non-rodents, pending follow-up on a couple of cases in the survey results. The group also initiated discussion on the reproductive toxicology survey results from each of the three ICH regions.

The next steps for the group will be to craft language for the “new” exploratory FIM section of the M3 guidance, to complete discussions of sections thought to be non-controversial, and to review and integrate survey results.
The SC supported the organisation of an interim meeting of the M3(R2) EWG in Washington D.C. to help the group with their aim of reaching Step 2 in Yokohama, in October 2007.

Q4B: Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC):
The Q4B EWG did not meet in Brussels. The SC endorsed the Q4B work plan, which was provided for their consideration in Brussels.

Q8: Pharmaceutical Development: The Rapporteur reported to the SC on the progress made on the Addendum to Q8 in Brussels. The Q8 EWG agreed high priority terms with the Q10 EWG. Substantial progress was made during the Brussels meeting.

Having reached initial consensus on a description of Quality by Design, this was further refined in the latest drafting activities. With this increasing activity, the EWG continued to revise the draft guideline by focusing on clarifying key terms and concepts, and ensuring consistency with the parallel development of Q10.

The SC noted that the Q8 EWG hoped to reach Step 2 in Yokohama in October 2007.

Q10: Pharmaceutical Quality System: In Brussels, the SC endorsed the Q10 Step 2 document. In order to allow for a six-month public consultation period for the Step 2 document, the SC agreed that the next meeting of the Q10 EWG take place in the spring of 2008. The EWG was tasked to develop a work plan for the next year, including the timeframe for reaching Step 4 for SC consideration.

E15: Pharmacogenomics: The E15 EWG did not meet in Brussels. The SC endorsed the E15 work plan, which was provided for their consideration in Brussels.

E14: The Clinical Evaluation of QT/QTc Interval Prolongation and ProArrhythmic Potential for Non-Antiarrhythmic Drugs Q&A document: The E14 IWG did not meet in Brussels. The SC endorsed the E14 work plan, which was provided for their consideration in Brussels.

E2F: Development Safety Update Report: The E2F EWG did not meet in Brussels. The SC endorsed the E2F work plan, which was provided for their consideration in Brussels.

Gene Therapy Discussion Group (GTDG): The GTDG did not meet in Brussels. In Brussels, the SC endorsed the GTDG work plan, including the organization of a workshop on viral/vector shedding to coincide with a meeting of the European Society of Gene Therapy in Rotterdam in October 2007. This would mean that the GTDG would meet in Rotterdam rather than Yokohama. The GTDG will submit a written report for SC consideration in Yokohama.
4. Communication about ICH:

In Chicago, in October 2006, the SC considered the organisation of smaller, more frequent and more focused ICH public meetings. These could either take place as one-day meetings at the end of ICH SC meetings, or as ICH-branded regional meetings in collaboration with other non-profit organisations.

In Brussels, the SC further discussed this approach and MHLW/JPMA presented a proposal to organise a one-day ICH public meeting on November 2, 2007 following the ICH meeting in Yokohama, Japan. This meeting would be the first regional ICH public meeting. The SC was invited to propose topics that should be discussed.

5. Dates of Next Meeting for 2007:
Oct. 27 – Nov. 1    Yokohama, Japan